US 4552751

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 050 480**
A2

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **81304805.5**

(51) Int. Cl.³: **A 61 K 9/24**, A 61 K 9/70

(22) Date of filing: **15.10.81**

(30) Priority: **17.10.80 JP 144503/80**

(43) Date of publication of application: **28.04.82 Bulletin 82/17**

(84) Designated Contracting States: **CH DE FR GB IT LI**

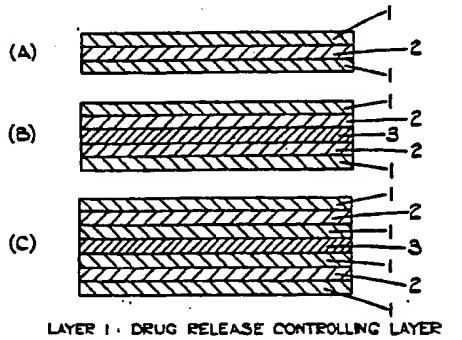
(71) Applicant: **ONO PHARMACEUTICAL CO., LTD., No. 14, Doshomachi 2-chome Higashi-ku, Osaka-shi Osaka (JP)**

(72) Inventor: **Kohji, Inaba, No. 395-52 Uzumasa, Neyagawa-shi Osaka (JP)**
Inventor: **Seiei, Sasatani, No. 20-8 Shibagaki 1-chome, Matsubara-shi Osaka (JP)**
Inventor: **Tatsushi, Koide, No. 4-31 Kawakita 3-chome, Fujiidera-shi Osaka (JP)**
Inventor: **Tamio, Nanya, No. 715-2 Uenoshiba-cho 5-chome, Sakai-shi Osaka (JP)**

(74) Representative: **Pearce, Anthony Richmond et al, Marks & Clerk Alpha Tower ATV Centre, Birmingham B1 1TT (GB)**

(54) **Long lasting multi-layered film preparation and process for its production.**

(57) The present invention provides multi-layered film preparations which comprise one or more water soluble polymer bases, one or more water insoluble polymer bases, one or more plasticizers and one or more prostaglandins, and optionally contain one or more organic acids, and they are composed of at least two drug release controlling layers (1) and one or more drug storing layers (2, 3). The multi-layered film preparations of the present invention are characterized by that the prostaglandin(s) containing therein exhibit the desired long-lasting release patterns at the concentration required for therapeutic purpose.



LAYER 1 : DRUG RELEASE CONTROLLING LAYER
LAYER 2 AND LAYER 3 : DRUG STORING LAYER

EP 0 050 480 A2

This invention relates to novel multi-layered film preparations and processes for the production thereof. More specifically, this invention relates to the multi-layered film preparations obtained by the combination of water soluble bases and water insoluble bases, characterized by that the prostaglandin or prostaglandins contained therein exhibit the desired long-lasting release patterns, further fully satisfying the purposes expected on prostaglandins aiming to lend themselves to uses as drug preparations which have high biological availability and are effective and safe, as well as the processes for the production thereof.

Various techniques for releasing drugs over an extended period of time have heretofore been reported in the literature. For instance, there are known coating methods to maintain release for an extended period of time as found mainly in oral tablets, intravaginally devices, drug release devices utilizing the osmotic pressure and dispensers utilizing semi-

permeable membranes or porous membranes etc. In more recent years, there have also been reported the development of polymers for achieving long-lasting release intended for topical applications, long-lasting films and containers for releasing the drug quantitatively by release from one side; in any case, however, they have disadvantages that high levels of techniques and equipment are required and that the form of that device (preparation) is retained even in the vital body (administration site) to give an extraneous feel to the human. Further, they also have such disadvantages that the expected drug efficacy is difficult to obtain because the stability of the active ingredient is adversely affected, the biological availability is low and the like.

Accordingly, an object of this invention is to provide multi-layered film preparations which have eliminated the disadvantages of the conventional techniques, that is, which, when prostaglandins are administered at the mucosal site, e.g. intravaginally, release the drug at the desired concentration and can make this release long lasting and further have improved the stability of the prostaglandins contained therein and in which the shape of the preparation is not retained at the administered site after administration.

Another object of this invention is to provide multi-layered film preparation which control the long-lasting release

by making the drug storing layers and the drug release controlling layers into the multi-layered form, and, therefore which release the active ingredient at the concentration required for therapeutic purpose.

In the drawings:

Fig. 1 (A), (B) and (C) are cross-sectional views showing an example of the multi-layered film preparations of this invention.

Fig. 2 is a graph showing the percent dissolution of the drug in various preparations.

The present invention provides multi-layered film preparation which comprise one or more water soluble polymer bases, one or more water insoluble polymer bases, one or more plasticizers and one or more prostaglandins, and optionally contain one or more organic acids, and they are composed of at least two drug release controlling layers and one or more drug storing layers.

The water soluble polymer bases included in this invention include biologically inactive, conventional water soluble polymers, preferably hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose etc., their average molecular

weights preferably being 10,000 - 400,000.

The water insoluble polymer bases included in this invention include biologically inactive, conventional water insoluble polymers, preferably cellulose acetate, vinyl acetate resin etc., their average degrees of polymerization preferably being 100 - 500.

The plasticizers included in this invention include biologically inactive, conventional plasticizers, preferably diethyl phthalate, butyl phthalyl butyl glycolate, glycerin triacetin, tributyrin, polyethylene glycol, polypropylene glycol, propylene glycol, diethylene glycol, triethylene glycol, dipropylene glycol etc.

The prostaglandins included in this invention include prostaglandin F compounds, prostaglandin E compounds and 6,9-thio-prostaglandin I_1 compounds having uterine contractile activity and/or effect to enlarge the uterocervical canal, and preferably they are prostaglandin F, prostaglandin E and 6,9-thio-prostaglandin I_1 analogues effective for induction of menstruation, abortion or induction of labour by intravaginal administration.

The organic acids included in this invention include such organic acids as citric acid, tartaric acid, succinic acid, stearic acid, palmitic acid etc., preferably citric acid, tartaric acid.

The multi-layered film preparations (hereinafter referred to as the preparations of this invention) are preferably administered to the mucosal tissue in the vital body, particularly

intravaginal administration is ideal.

The important characteristics of the preparations of this invention are more fully described by setting forth some examples as shown in Fig. 1 (A), (B) and (C) (which are intended to give more understanding thereof but not to limit this invention to these examples).

The preparations of this invention comprises at least two drug release controlling layers (Layer 1 in Fig. 1) and one or more drug storing layers (Layer 2 and Layer 3 in Fig. 1), and the two upper and lower layers on the outside are the drug release controlling layers. The size is preferably such that the surface area (the sum of the surface areas of the two upper and lower surfaces) is 1.5 - 30 cm^2 and the thickness is 0.1 - 3 mm, especially the size of 4 - 15 cm^2 in surface area and 0.2 - 2 mm in thickness being desired.

The drug release controlling layers comprises (A) one or more water soluble polymer compounds, (B) one or more water insoluble

polymer compounds and (C) one or more plasticizers, and on administration to the mucosal tissue in the vital body, they are swollen and dissolved or decomposed with the body liquid. By this, the body liquid permeates into the drug storing layer or layers, and the drug contained therein is leached out. The drug release is controlled by the physical properties that the drug release controlling layers are dissolved or decomposed with the body liquid.

In order to obtain the release rate of the drug and the long-lasting properties of the release suitable for the kind and properties of the drug contained in the preparations of this invention, and for the expected drug efficacy etc., this is effected by i) meeting the purposes by changing the constitutional ratio of the water soluble polymer compounds to water insoluble polymer compounds constituting the drug release controlling layers thereby properly establishing the physical properties of being dissolved or decomposed with the body liquid, and/or by ii) meeting the purposes by properly establishing the ratio of the surface area to thickness of the drug release controlling layers and/or by iii) meeting the purposes by properly establishing the number of the drug release controlling layers [for example, Fig. 1 (C)]. In the case of iii), the thicknesses of the respective layers may be the same or different. In addition, the kinds and the constitutional ratios of the polymer compounds constituting the respective layers may be the same or different.

While the drug release controlling layers most often do not contain any drug, it is possible to incorporate a minor amount

of the drug in the drug release controlling layers where it is necessary to release the drug in the earlier stage after administration.

The drug storing layers comprise one or more water soluble polymer compounds, or one or more of each of (A) water soluble polymer compounds and (B) plasticizers, or one or more of each of (A) water soluble polymer compounds, (B) water insoluble polymer compounds and (C) plasticizers, and contain required amounts of the drug.

The release rate of the drug and the long-lasting properties of the release suitable for the kind and properties of the drug contained in the drug storing layers and for the expected drug efficacy etc. may also be achieved by making the drug storing layers in the following manner:

i) using a water soluble polymer compound or compounds and water insoluble polymer compound or compounds, and properly establishing the constitutional ratio thereof, and/or ii) making two or more drug storing layers having different kinds and constitutional ratios of the constituting polymer compounds [for example, Fig. 1 (B) or (C)], and/or iii) making two or more drug storing layers having different levels of the drug [for example, Fig. 1 (B) or (C)], and/or iv) properly establishing the thickness of each drug storing layer.

Further, in this invention, it is also possible to contain two or more drugs having different pharmacological properties in separate drug storing layers to provide medicines ideal from an aspect of the drug efficacy. For example, for the purpose of

induction of labour or abortion, five-layered or seven-layered film preparations which contain a prostaglandin having a strong effect to enlarge the uterocervical canal such as 16,16-dimethyl-trans-Δ^2-PGE_1 methyl ester (hereinafter simply referred to as ONO-802) in the drug storing layer 2 in (B) or (C) of Fig. 1 and a prostaglandin having a strong uterine contractile effect such as 16,16-dimethyl-6,9-thio-PGI_1 methyl ester in the drug storing layer 3 enlarge the uterocervical canal and thereafter bring about contraction of the uterus, and therefore ideal.

In the drug release controlling layers or the drug storing layers, when the water soluble polymer compound(s) and the water insoluble polymer compound(s) are employed in combination, the constitutional ratio (by weight) thereof may be freely established in the range of 1 - 9 of the water soluble polymer compound(s) to 9 - 1 of the water insoluble polymer compound(s), and particularly preferred is 5 - 9 of the former to 5 - 1 of the latter.

The water soluble polymer compounds are commercially available in several specifications classified depending on the molecular weight of the polymer contained, and by using a different specification or by employing two or more of these specifications in combination, a more advantageous preparation meeting the purposes may be obtained. Preferably, the water soluble polymer compound is contained at a proportion of 10 - 80% in the preparation of the present invention.

Also with the water insoluble polymer compounds, there are several products of different specifications on the market, a similar effect may be achieved by using a different specification

or by employing two or more of these in combination. Preferably, the water insoluble polymer compound is contained at a proportion of 10 - 80% in the preparation of the present invention.

Further, in this invention, since it is possible to make a soft, flexible film preparation suitable for the administration site by changing the kinds of the plasticizers to be used or by employing two or more plasticizers in combination, the disadvantages with the conventional film preparations can be eliminated, a physical difficulty in the administration site may be prevented and an effect to enhance the release properties of the active ingredient is obtained. Preferably, the plasticizer is contained at a proportion of 10 - 30% in the preparation of the present invention.

Still further in this invention, although stability of prostaglandin(s) can be adequately maintained even without incorporating an organic acid in the preparations sufficiently to provide products, addition of an organic acid gives more stable prostaglandin preparations. Though the organic acid to be added is not particularly restricted, citric acid, tartaric acid, succinic acid etc. are effective, and among these citric acid or tartaric acid is especially preferred. The amount of the organic acid to be added is preferable such that it is added to the preparation at a proportion of 0.01 - 0.5%, particularly preferably 0.05 - 0.3%.

The features of the preparations obtained according to this invention are as follows:

(1) By combining properly the drug storing layers and the

drug release controlling layers, the release of the drug may be controlled according to the desired purpose to render it long-lasting.

(2) They may be applied to the site where the active ingredient are absorbed through the mucous membrane.

(3) Since the form of the film can be fully dissolved or decomposed with the body liquid, the physical difficulty may be prevented thus giving no extraneous feeling.

(4) During the film formation step, by addition of an organic acid, even unstable materials are hardly decomposed, and therefore stability can be retained for an extended period of time.

(5) Since a constant release pattern of the drug is obtained regardless of the individuals, high effectiveness is exhibited at a low dosage level of the drug.

(6) Since the biological availability is high and hence a dosage level of the drug may be low, there is no possibility for overdose and therefore safer preparations may be presented.

The process for the production of the preparations of this invention may be exemplified by a method which comprises preparing a drug release controlling layer solution (a solution for preparing drug release controlling layers) and a drug storing layer solution (a solution for preparing drug storing layers) respectively, and thereafter either 1) removing the organic solvents of the respective solutions by drying to prepare film-formed layers respectively, and mounting them, one on another, by a dry laminate or wet laminate method to prepare

the desired multi-layered film preparation or 2) coating the drug storing layer solution on a film obtained by removing the organic solvent of the drug release controlling layer solution by drying, then removing the organic solvent by drying, and repeating these operations to prepare respective film-formed layers successively, thereby preparing the desired multi-layered film preparation.

The drug release controlling layer solution may be obtained by dissolving one or more water insoluble polymer compounds and one or more plasticizers in an organic solvent and, when a transparent solution is formed, adding one or more water soluble polymer compounds thereto and dissolving it over an adequate period of time, and if desired, adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent and further allowing it to stand and adequately deaerating it.

The drug storing layer solution may be obtained, (i) by dissoving one or more water soluble polymer compounds or a mixture of one or more water soluble polymer compounds and one or more water insoluble polymer compounds in an organic solvent and, when a transparent solution is formed, adding one or more plasticizers according to the desirability, and adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent, stirring uniformly, allowing it to stand and adequately deaerating it, (ii) by dissolving one or more water insoluble polymer compounds and one or more plasticizers in an organic solvent and,

when a transparent solution is formed, adding one or more water soluble polymer compounds thereto and dissolving it over an adequate period of time, and adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent, stirring uniformly and further allowing it to stand and adequately deaerating it, or (iii) by dissolving one or more water soluble polymer compounds and one or more plasticizers in an organic solvent and, when a transparent solution is formed, adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent, stirring uniformly and allowing it to stand and adequately deaerating it.

While the organic solvent to be used may be any as long as it can dissolve the respective components for the preparation and is inert to them, methanol, ethanol, acetone, methylene chloride etc. are preferred, and they may be used either alone or in combination.

As the drying method, a conventional method such as standing at room temperature, drying with moderate heating, fluidized bed drying etc. can be used, but from the viewpoint of stability of prostaglandins drying at elevated temperatures is not proper. A temperature of between room temperature and 60°C is preferred. Therefore, it is preferred to dry using a device which can control the temperature and the air flow.

The size, shape, thickness etc. of the multi-layered film preparation may be properly established depending on the pharmacological properties of the prostaglandin contained therein, the purpose for use etc., and may be prepared using a conventional process for producing multi-layered film preparations.

This invention is more fully described by the following examples and experiment examples but this invention should in no way be restricted thereto.

Example 1

1) Preparation of a drug release controlling layer solution: 1.2 g of vinyl acetate resin, 200 mg of glycerin and 200 mg of triacetin were added to 40 ml of methanol and then stirred until transparent. Thereafter, 2.4 g of hydroxypropyl cellulose was added, and the solution was stirred and allowed to stand for effecting deaeration.

2) Preparation of a drug storing layer solution: 1.88 g of hyroxypropyl cellulose, 10 mg of glycerin and 100 mg of triacetin were added to 20 ml of methanol and stirred. To the resulting solution was added a solution of 10 mg of ONO-802 and 3 mg of tartaric anhydride in 10 ml of methanol, and the solution was stirred and then allowed to stand for effecting deaeration.

3) Production of multi-layered film preparations: A) 10 ml of the drug release controlling layer solution was dried at room temperature by a casting method, and then 15 ml of the drug storing layer solution was poured and similarly dried. Finally, 10 ml of the drug release controlling layer solution was poured and similarly dried to obtain a three-layered film preparation of

about 0.9 mm in thickness. B) 10 ml portions of the drug release controlling layer solution were dried at room temperature using a casting method to obtain two films. The thus obtained two films were laminated with a film, obtained by similarly drying 15 ml of the drug storing layer solution, placed therebetween to obtain a three-layered film preparation of about 0.9 mm in thickness.

Example 2

A three-layered film preparation of about 0.9 mm in thickness was obtained similarly as in Example 1, except that the vinyl acetate resin employed in Example 1 was replaced by cellulose acetate, the hydroxypropyl cellulose by hydroxypropyl methyl cellulose and the glycerin by butyl phthalyl butyl glycolate.

Example 3

A three-layered film preparation of about 0.9 mm in thickness was obtained similarly as in Example 1, except that the hdryoxypropyl cellulose employed in Example 1 was replaced by polyvinylpyrrolidone.

Example 4

1) Using 130 mg of vinyl acetate resin, 70 mg of glycerin, 70 mg of triacetin, 20 ml of methanol and 1.07 g of hydroxypropyl cellulose, similar procedures as in 1) and 3) B) of Example 1 were repeated to obtain two films.

2) 70 mg of vinyl acetate resin, 30 mg of glycerin and 30 mg of triacetin were added to 15 ml of methanol and stirred until transparent, after which 538.5 mg of hydroxypropyl cellulose was added and stirred. To this solution was added a solution

of 1.5 mg of 16,16-dimethyl-6,9-thio-PGI_1 methyl ester dissolved in 5 ml of methanol, and the solution was stirred and allowed to stand for effecting deaeration. The resulting solution was dried at room temperature by a casting method to obtain a film.

3) Using 1.26 g of hydroxypropyl cellulose, 65 mg of triacetin, 65 mg of glycerin, 15 ml of methanol, 2.5 mg of ONO-802, 2 mg of tartaric anhydride and 5 ml of methanol, similar procedures as in 2) and 3) B) of Example 1 were repeated to obtain two films.

4) Using a laminating method, the film obtained in 1), the film obtained in 3) the film obtained in 2), the film obtained in 3) and the film obtained 1) were laminated successively to obtain a five-layered film preparation of about 1.0 mm in thickness.

Example 5

A five-layered film preparation of about 1.0 mm in thickness was obtained similarly as in Example 4, except that the hydroxypropyl cellulose employed in Example 4 was replaced by polyvinylpyrrolidone.

Example 6

1) Using 300 mg of vinyl acetate resin, 150 mg of glycerin, 150 mg of triacetin, 30 ml of methanol and 2.4 g of hydroxypropyl cellulose, similar procedures as in 1) of Example 1 were repeated to obtain about 30 ml of the solution.

2) A solution of 5 mg of ONO-802 and 1.5 mg of tartaric anhydride dissolved in one ml of methanol was added to 10 ml of the solution obtained in 1), stirred and then allowed to stand for effecting deaeration.

3) Using 20 ml of the solution obtained in 1) and the solution obtained in 2), procedures similar as in 3) B) of Example 1 were repeated to obtain a three-layered film preparation of about 0.9 mm in thickness.

Experiment Example 1

In order to compare the following preparations: the multi-layered film preparations produced in Examples 1 and 6; a single-layered film preparation employing a water soluble polymer compound (prepared as described hereafter; and simply referred to as HPC film); and a single-layered film preparation employing a water soluble polymer compound and a water insoluble polymer compound (prepared as described hereafter; and simply referred to as HPTG film), for the release rate of the drug and the long-lasting properties of the release, a dissolution test was conducted according to the USP paddle method. The results of the experiment are shown in Table 1 and Fig. 2.

Preparation of HPC film: A solution of 199.5 mg of hydroxypropyl cellulose in 2 ml of ethanol was stirred until a transparent solution was formed. The above cellulose solution was added to a solution of 0.2 mg of ONO-802 and 0.3 mg of tartaric anhydride in 1 ml of ethanol and the mixture was stirred uniformly. The solution thus obtained was dried at low temperature by a casting method to obtain HPC film.

Preparation of HPTG film: A solution of 20 mg of vinyl acetate resin, 10 mg of glycerin and 10 mg of triacetin in 2 ml of methanol was stirred until a transparent solution was formed.

30 mg of HPC-M (a registered Trade Mark; and a kind of hydroxypropyl cellulose) and 130 mg of HPC-L (a registered Trade Mark; and a kind of hydroxypropyl cellulose) were added thereto and the solution was stirred uniformly. To the solution thus obtained was added a solution of 0.2 mg of ONO-802 and 0.3 mg of tartaric anhydride in 1 ml of methanol and the solution was stirred uniformly. The solution thus obtained was dried at room temperature by a casting method to obtain HPTG film.

Table 1

Percent Dissolution (%)
in Various Preparations

Sample	Dissolution Time (hr)						
	0.5	1	2	3	4	5	6
HPC Film	97.6	100					
HPTG Film	23.1	57.0	98.3	100			
Film of Example 6	7.0	15.9	35.8	59.6	80.0	90.0	95.0
Film of Example 1	2.9	6.4	11.2	23.3	39.6	55.6	65.2

Experiment Example 2

The multi-layered film preparation produced in Example 1 and HPTG film were compared for the uterine contractile activity which is the pharmacological activity of ONO-802 in non-anesthetized rats. In this test, each preparation cut into a size corresponding to the indicated dosage was administered. The results of the experiment are shown in Table 2.

Table 2

Comparison of Uterine Contractile Activity in Various Preparations

(Intravaginal Administration to Non-anesthetized Rats)

Dosage of ONO-802 (μg/kg)	Film of Example 1		HPTG Film	
	Effective Ex. /Total Ex.	Duration (min.)	Effective Ex. /Total Ex.	Duration (min.)
200	8/8	600 - 720	8/8	400 - 450
400	8/8	720 - 780	8/8	450 - 500
800	8/8	840 - 900	6/6	470 - 540

The duration of the uterine contractile activity was greatly prolonged with the preparation of Example 1. The intensity of the activity of HPTG film is greater than that of the preparation of Example 1 at the same dose. About 400 μg dosage of the preparation of Example 1 corresponded to the 100 μg dosage of HPTG film. In the case of the dosage levels of the preparation of Example 1, a weak pattern was exhibited at 200 μg, while medium-level lasting pattern were exhibited both at 400 and 800 μg.

Claims

1. A multi-layered film preparation which comprises (A) one or more water soluble polymer compounds, (B) one or more water insoluble polymer compounds, (C) one or more plasticizers and (D) one or more prostaglandins, and optionally contains one or more organic acids.

2. A multi-layered film preparation according to claim 1 which comprises one or more drug storing layers and two or more drug release controlling layers.

3. A multi-layered film preparation according to claim 1 which contains prostaglandins in the drug storing layer or layers.

4. A multi-layered film preparation according to claim 1 which contains prostaglandins in the drug storing layer or layers and at least one drug release controlling layer.

5. A multi-layered film preparation according to claim 1 which has a drug storing layer or layers comprising one or more water soluble polymer compounds and one or more prostaglandins and optionally containing one or more plasticizers.

6. A multi-layered film preparation according to claim 1 which has a drug storing layer or layers comprising (A) one or more water soluble polymer compounds, (B) one or more water insoluble polymer compounds, (C) one or more plasticizers and (D) one or more prostaglandins.

7. A multi-layered film preparation according to claim 1 which has drug release controlling layers compriseing (A) one or more water soluble polymer compounds, (B) one or more water

insoluble polymer compounds and (C) one or more plasticizers.

8. A multi-layered film preparation according to claim 1 which has a surface area of 1.5 - 30 cm^2 and a thickness of 0.1 - 3 mm.

9. A multi-layered film preparation according to claim 1 in which the water soluble polymer compound is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropyl methyl cellulose.

10. A multi-layered film preparation according to claim 1 in which the water insoluble polymer compound is cellulose acetate or vinyl acetate resin.

11. A multi-layered film preparation according to claim 1 in which the plasticizer is diethyl phthalate, butyl phthalyl butyl grycolate, glycerin, triacetin, tributyrin, polyethylene glycol, polypropylene grycol, propylene glycol, diethylene glycol, triethylene glycol or dipropylene glycol.

12. A multi-layered film preparation according to claim 1 in which the prostaglandin is prostaglandin F, prostaglandin E or 6,9-thio-prostaglandin I_1.

13. A multi-layered film preparation according to claim 1 in which the organic acid is citric acid or tartaric acid.

14. A multi-layered film preparation according to claim 1 in which the water soluble polymer compound is contained at a proportion of 10 - 80%.

15. A multi-layered film preparation according to claim 1 in which the water insoluble polymer compound is contained at a proportion of 10 - 80%.

16. A multi-layered film preparation according to claim 1 in which the plasticizer is contained at a proportion of 10 - 30%.

17. A multi-layered film preparation according to claim 1 in which the organic acid is contained at a proportion of 0.01 - 0.5%.

18. A three-layered film preparation according to claim 1 which has two drug release controlling layers comprising vinyl acetate resin, glycerin, triacetin and hydroxypropyl cellulose, and therebetween one drug storing layer comprising hydroxypropyl cellulose, glycerin, triacetin, ONO-802 and tartaric anhydride.

19. A three-layered film preparation according to claim 1 which has two drug release controlling layers comprising cellulose acetate, butyl phthalyl butyl grycolate, triacetin and hydroxypropyl methyl cellulose, and therebetween one drug storing layer comprising hydroxypropyl methyl cellulose, butyl phthalyl butyl grycolate, triacetin, ONO-802 and tartaric anhydride.

20. A three-layered film preparation according to claim 1 which has two drug release controlling layers comprising vinyl acetate resin, glycerin, triacetin and polyvinylpyrrolidone, and therebetween one drug storing layer comprising polyvinylpyrrolidone, glycerin, triacetin, ONO-802 and tartaric anhydride.

21. A five-layered film preparation according to claim 1 which has the structure mounting successively (1) a drug release controlling layer comprising vinyl acetate resin, glycerin, triacetin and hydroxypropyl cellulose, (2) a drug storing layer comprising hydroxypropyl cellulose, glycerin, triacetin, ONO-

802 and tartaric anhydride, (3) a drug storing layer comprising vinyl acetate resin, glycerin, triacetin, hydroxypropyl cellulose and 16,16-dimethyl-6,9-thio-PGI_1 methyl ester, (4) the drug storing layer as mentioned in (2), and (5) the drug release controlling layer as mentioned in (1).

22. A five-layered film preparation according to claim 1 which has the structure mounting successively (1) a drug release controlling layer comprising vinyl acetate resin, glycerin, triacetin and polyvinylpyrrolidone, (2) a drug storing layer comprising polyvinylpyrrolidone, glycerin, triacetin, ONO-802 and tartaric anhydride, (3) a drug storing layer comprising vinyl acetate resin, glycerin, triacetin, polyvinylpyrrodidone and 16,16-dimethyl-6,9-thio-PGI_1 methyl ester, (4) the drug storing layer as mentioned in (2), and (5) the drug release controlling layer as mentioned in (1).

23. A three-layered film preparation according to claim 1 which has two drug release controlling layers comprising vinyl acetate resin, glycerin, triacetin and hydroxypropyl cellulose, and therebetween one drug storing layer comprising vinyl acetate resin, glycerin, triacetin, hydroxypropyl cellulose, ONO-802 and tartaric anhydride.

24. A process for producing multi-layered film preparations which is characterized by using a laminating method to make a multi-layered film preparation from a film or films

(drug storing layer or layers) obtained by dissolving water soluble polymer compound(s) and prostaglandin(s) in an organic solvent, further adding or not adding plasticizer(s) and/or organic acid(s) thereto, thoroughly stirring, and thereafter drying to remove the organic solvent by a conventional method and films (drug release controlling layers) obtained by dissolving water soluble polymer compound(s), water insoluble polymer compound(s) and plasticizer(s) in an organic solvent, further adding or not adding prostaglandin(s) and/or organic acid(s) thereto, thoroughly stirring, and thereafter drying to remove the organic solvent by a conventional method.

25. A process for producing multi-layered film preparations which is characterized by using a laminating method to make a multi-layered film preparation from a film or films (drug storing layer or layers) obtained by dissolving water soluble polymer compound(s), water insoluble polymer compound(s), prostaglandin(s) and plasticizer(s) in an organic solvent, further adding or not adding organic acid(s) thereto, thoroughly stirring, and thereafter drying to remove the organic solvent by a conventional method and films (drug release controlling layers) obtained by dissolving water soluble polymer compound(s), water insoluble polymer compound(s) and plasticizer(s) in an organic solvent, further adding or not adding prostaglandin(s) and/or organic acid(s) thereto, thoroughly stirring, and thereafter drying to remove the organic solvent by a conventional method.

0050480

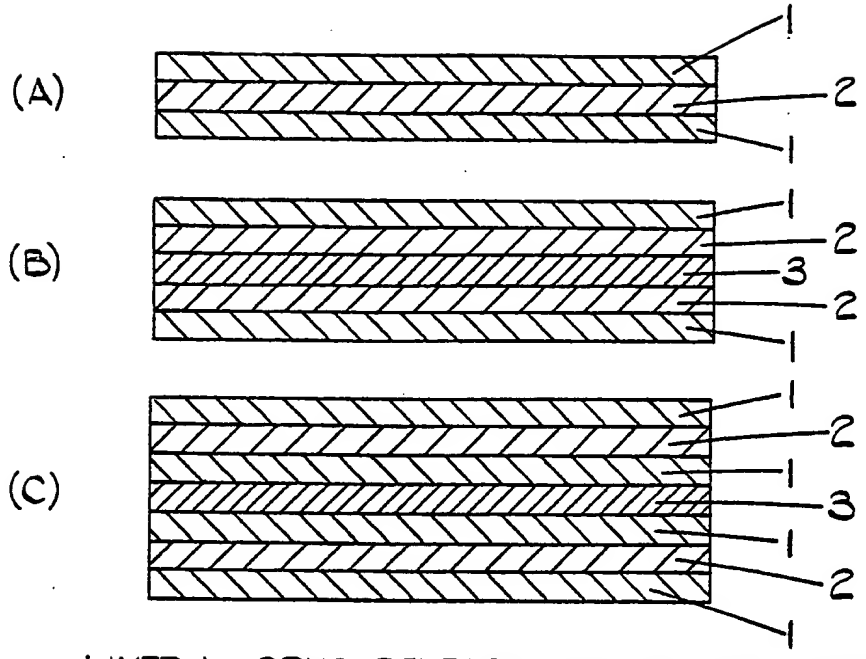


FIG.1.

LAYER 1 : DRUG RELEASE CONTROLLING LAYER
LAYER 2 AND LAYER 3 : DRUG STORING LAYER

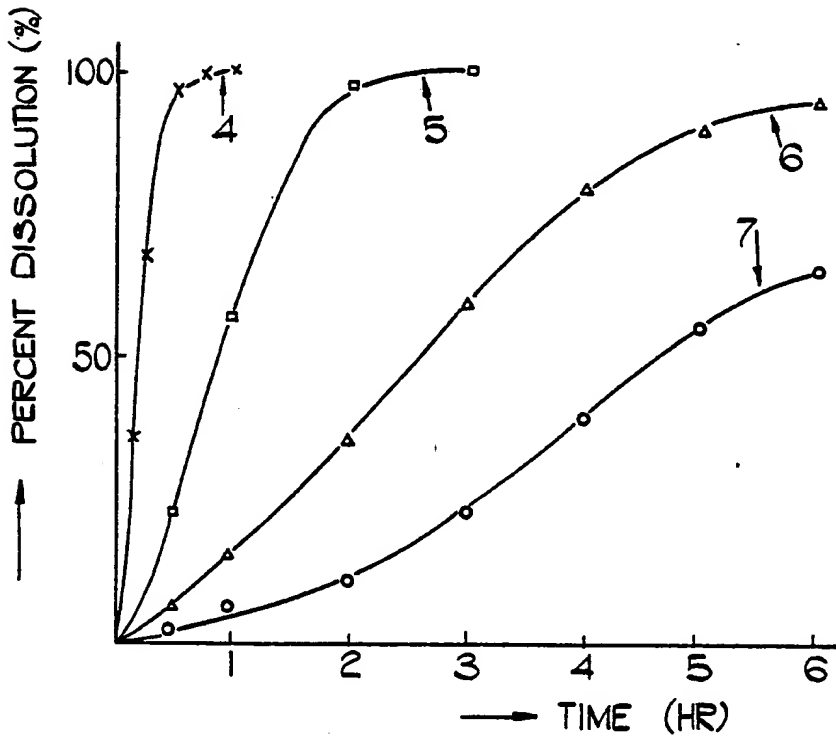


FIG.2.

4: HPC FILM PREPARATION
5: HPTG FILM PREPARATION
6: FILM PREPARATION OF EXAMPLE 6
7: FILM PREPARATION OF EXAMPLE 1

(19) Europäisches Patentamt
European Patent Office
Office européen d s brevets

(11) Publication number: **0 050 480**
B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **22.01.86**

(51) Int. Cl.⁴: **A 61 K 9/24**, A 61 K 9/70

(21) Application number: **81304805.5**

(22) Date of filing: **15.10.81**

(54) Long lasting multi-layered film preparation and process for its production.

(30) Priority: **17.10.80 JP 144503/80**

(43) Date of publication of application:
28.04.82 Bulletin 82/17

(45) Publication of the grant of the patent:
22.01.86 Bulletin 86/04

(84) Designated Contracting States:
CH DE FR GB IT LI

(56) References cited:
RESEARCH DISCLOSURE, May 1980, pages 164-165, no. 19319; "Film shaped vaginal dispensers containing prostaglandins for prolonged controlled release"

CHEMICAL ABSTRACTS, vol. 93, no. 19, 10th November 1980, page 357, no. 191993d, Columbus Ohio (USA); M. DONBROW et al.: "Zero order drug delivery from double-layered porous films: release rate profiles from ethyl cellulose, hydroxypropyl cellulose, and polyethylene glycol mixtures"

(73) Proprietor: **ONO PHARMACEUTICAL CO., LTD.**
No. 14, Doshomachi 2-chome Higashi-ku
Osaka-shi Osaka (JP)

(72) Inventor: **Kohji, Inaba**
No. 395-52 Uzumasa
Neyagawa-shi Osaka (JP)
Inventor: **Seiei, Sasatani**
No. 20-8 Shibagaki 1-chome
Matsubara-shi Osaka (JP)
Inventor: **Tatsushi, Koide**
No. 4-31 Kawakita 3-chome
Fujiidera-shi Osaka (JP)
Inventor: **Tamio, Nanya**
No. 715-2 Uenoshiba-cho 5-chome
Sakai-shi Osaka (JP)

(74) Representative: **Pearce, Anthony Richmond et al**
Marks & Clerk Alpha Tower Suffolk Street Queensway Birmingham B1 1TT (GB)

Courier Press, Leamington Spa, England.

EP 0 050 480 B1

D scription

This invention relates to n vel multi-layered film preparations and processes for the production th reof. M re specifically, this invention relates to the multi-layered film preparati ns obtained by the combination of water soluble bases and water insoluble bases, characterized by that the prostaglandin or prostaglandins contained therein exhibit the desired long-lasting release patterns, further fully satisfying the purposes expected of prostaglandins aiming to lend themselves to uses as drug preparations which have high biological availability and are effective and safe, as well as the processes for the production thereof.

Various techniques for releasing drugs over an extended period of time have heretofore been reported in the literature. For instance, there are known coating methods to maintain release for an extended period of time as found mainly in oral tablets, intravaginal devices, drug release devices utilizing osmotic pressure and dispensers utilizing semi-permeable membranes or porous membranes. In more recent years, there have also been reported the developments of polymers for achieving long-lasting release intended for topical applications, long-lasting films and containers for releasing the drug quantitatively by release from one side; in any case, however, they have disadvantages that high levels of techniques and equipment are required and that the form of that device (preparation) is retained even in the vital body (administration site) to give an extraneous feel to the human. Further, they also have such disadvantages that the expected drug efficiency is difficult to obtain because the stability of the active ingredients is adversely affected or the biological availability is low.

Double layered porous film preparations containing drugs have been previously proposed (J. Pharm Pharmacol 1980, 32 p 463). These films consist of a drug storing layer and drug release controlling layers. However, such preparations do not dissolve completely and the administration form of the film remains at the administration site after release and so must be removed after the drug has been released.

Research Disclosure 19319 discloses single film compositions containing a prostaglandin as a drug. In these preparations, the drug is released as the single film dissolves and thus results in non-linear release over a relatively short time.

Accordingly, an object of this invention is to provide multi-layered film preparations which have eliminated the disadvantages of the conventional techniques, that is, which, when prostaglandins are administered at the mucosal site, e.g. intravaginally, release the drug at the desired concentration and can make this release long lasting and further have improved the stability of the prostaglandins contained therein and in which the shape of the preparation is not retained at the administered site after administration.

Another object of this invention is to provide multi-layered film preparation which control the long-lasting release by making the drug storing layers and the drug release controlling layers into the multi-layered form, and therefore which release the active ingredient at the concentration required for therapeutic purposes.

According to the present invention there is provided a multi-layered film preparation having at least one drug-storing layer including at least one water-soluble polymer compound; drug release-controlling layers disposed on opposite sides of the drug-storing layer or layers, each of said drug release-controlling layers including at least one water-soluble polymer compound, at least one water-insoluble polymer compound and at least one plasticizer; and a drug in said at least one drug-storing layer, characterized in that the drug is at least one prostaglandin and said drug-storing and drug-release controlling layers are formulated so as to dissolve or decompose totally during administration at a mucosal site, and the weight ratio of water-soluble polymer to water-insoluble polymer is in the range 9:1 to 1:1.

In the drawings:

Fig. 1(A), (B) and (C) are cross-sectional views showing an example of the multi-layered film preparations of this invention.

Fig. 2 is a graph showing the percent dissolution of the drug in various preparations.

The multi-layered film preparation according to the present invention preferably includes one or more organic acids to stabilise said at least one prostaglandin.

The water-soluble polymer bases included in this invention include biologically inactive, conventional water soluble polymers, preferably, hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose etc., their average molecular weights preferably being 10,000—400,000.

The water insoluble polymer bases included in this invention include biologically inactive, conventional water insoluble polymers, preferably cellulose acetate, vinyl acetate resin etc., their average degrees of polymerization preferably being 100—500.

The plasticizers included in this invention include biologically inactive, conventional plasticizers, preferably diethyl phthalate, butyl phthalyl butyl glycolate, glycerin triacetin, tributyrin, polyethylene glycol, polypropylene glyc l, pr pylene glyc l, diethylen glycol, triethylene glycol and dipropylene glycol.

The prostaglandins included in this invention include pr staglandin F compounds, prostaglandin E compounds and 6,9-thi -prostaglandin I_1 compounds having uterine contractile activity and/or effect to enlarge the uterocervical canal, and preferably they are prostaglandin F, pr staglandin E and 6,9-thio-prostaglandin I_1 analogues effective f r induction or menstruation, abortion or inducti n of labour by intravaginal administration.

The organic acids included in this invention include such rganic acids as citric acid, tartaric acid, succinic acid, stearic acid and palmitic acid, pref rably citric acid or tartaric acid.

The multi-layered film preparati ns (hereinafter referred to as th preparations of this invention) are preferably administered t the mucosal tissu in th vital body, particularly intravaginal administration is ideal.

The important characteristics of the preparations of this invention are more fully described by setting forth some examples as shown in Fig. 1(A), (B) and (C) (which are intended to give more understanding thereof but not to limit this invention to these examples).

The preparations of this invention comprises at least two drug release controlling layers (Layer 1 in Fig. 1) and one or more drug storing layers (Layer 2 and Layer 3 in Fig. 1), and the two upper and lower layers on the outside are the drug release controlling layers. The size is preferably such that the surface area (the sum of the surface areas of the two upper and lower surfaces) is 1.5—30 cm^2 and the thickness is 0.1—3 mm, especially the size of 4—15 cm^2 in surface area and 0.2—2 mm in thickness being desired.

The drug release controlling layers comprises (A) at least one water soluble polymer compound, (B) at least one water insoluble polymer compound and (C) at least one plasticizer, and on administration to the mucosal tissue in the vital body, they are swollen and dissolved or decomposed with the body liquid. By this, the body liquid permeates into the drug storing layer or layers, and the drug contained therein is leached out. The drug release is controlled by the physical properties that the drug release controlling layers are dissolved or decomposed with the body liquid.

In order to obtain the release rate of the drug and the long-lasting properties of the release suitable for the kind and properties of the drug contained in the preparations of this invention, and for the expected drug efficacy etc., this is effected by i) meeting the purposes by changing the constitutional ratio of the water soluble polymer compounds to water insoluble polymer compounds constituting the drug release controlling layers thereby properly establishing the physical properties of being dissolved or decomposed with the body liquid, and/or by ii) meeting the purposes by properly establishing the ratio of the surface area to thickness of the drug release controlling layers and/or by iii) meeting the purposes by properly establishing the number of the drug release controlling layers [for example, Fig. 1(C)]. In the case of iii), the thicknesses of the respective layers may be the same or different. In addition, the kinds and the constitutional ratios of the polymer compounds constituting the respective layers may be the same or different.

While the drug release controlling layers most often do not contain any drug, it is possible to incorporate a minor amount of the drug in the drug release controlling layers where it is necessary to release the drug in the earlier stage after administration.

The drug storing layers comprise at least one water soluble polymer compound, or at least one of each of (A) water soluble polymer compounds and (B) plasticizers, or at least one of each of (A) water soluble polymer compounds, (B) water insoluble polymer compounds and (C) plasticizers, and contain required amounts of the drug.

The release rate of the drug and the long-lasting properties of the release suitable for the kind and properties of the drug contained in the drug storing layers and for the expected drug efficacy etc. may also be achieved by making the drug storing layers in the following manner:

i) using a water soluble polymer compound or compounds and water insoluble polymer compound or compounds, and properly establishing the constitutional ratio thereof, and/or ii) making two or more drug storing layers having different kinds and constitutional ratios of the constituting polymer compounds [for example, Fig. 1(B) or (C)], and/or iii) making two or more drug storing layers having different levels of the drug [for example, Fig. 1(B) or (C)], and/or iv) properly establishing the thickness of each drug storing layer.

Further, in this invention, it is also possible to contain two or more drugs having different pharmacological properties in separate drug storing layers to provide medicines ideal from an aspect of the drug efficacy. For example, for the purpose of induction of labour or abortion, five-layered or seven-layered film preparations which contain a prostaglandin having a strong effect to enlarge the uterocervical canal such as 16,16 - dimethyl - trans - 4^2 - PGE_1 methyl ester (hereinafter simply referred to as ONO-802) in the drug storing layer 2 in (B) or (C) of Fig. 1 and a prostaglandin having a strong uterine contractile effect such as 16,16 - dimethyl - 6,9 - thio - PGI_1 methyl ester in the drug storing layer 3 enlarge the uterocervical canal and thereafter bring about contraction of the uterus.

In the drug release controlling layers or the drug storing layers, when the water soluble polymer compound(s) and the water insoluble polymer compound(s) are employed in combination, the constitutional ratio (by weight) thereof is freely established in the range of 5—9 of the water soluble polymer compound(s) to 5—1 of the water insoluble polymer compound(s).

The water soluble polymer compounds are commercially available in several specifications classified depending on the molecular weight of the polymer contained, and by using a different specification or by employing two or more of these specifications in combination, a more advantageous preparation meeting the purp ses may be obtained. Preferably, the water soluble polymer compound is contained at a proportion of 10—80% in the pr paration of the present inventi n.

Also with the water insoluble p lymer compounds, there ar sev ral products of different specifications on the market, a similar effect may be achieved by using a different specification or by employing two or more of these in combination.

Further, in this invention, since it is possible to make a soft, flexible film preparation suitable for the administration site by changing the kinds of the plasticizers to be used or by employing two or more plasticizers in combination, the disadvantages with the conventional film preparations can be eliminated, a physical difficulty in the administration site may be prevented and an effect to enhance the release properties of the active ingredient is obtained. Preferably, the plasticizer is contained at a proportion of 10—30% in the preparation of the present invention.

Still further in this invention, although stability of prostaglandin(s) can be adequately maintained even without incorporating an organic acid in the preparation sufficiently to provide products, addition of an organic acid gives more stable prostaglandin preparations. Though the organic acid to be added is not particularly restricted, citric acid, tartaric acid and succinic acid are effective, and among these citric acid or tartaric acid is especially preferred. The amount of the organic acid to be added is preferably such that it is added to the preparation at a proportion of 0.01—0.5%, particularly preferably 0.05—0.3%.

The features of the preparations obtained according to this invention are as follows:

(1) By combining properly the drug storing layers and the drug release controlling layers, the release of the drug may be controlled according to the desired purpose to render it long-lasting.

(2) They may be applied to the site where the active ingredient are absorbed through the mucous membrane.

(3) Since the form of the film can be fully dissolved or decomposed with the body liquid, the physical difficulty may be prevented thus giving no extraneous feeling.

(4) During the film formation step, by addition of an organic acid, even unstable materials are hardly decomposed, and therefore stability can be retained for an extended period of time.

(5) Since a constant release pattern of the drug is obtained regardless of the individuals, high effectiveness is exhibited at a low dosage level of the drug.

(6) Since the biological availability is high and hence a dosage level of the drug may be low, there is no possibility for overdose and therefore safer preparations may be presented.

The process for the production of the preparations of this invention may be exemplified by a method which comprises preparing a drug release controlling layer solution (a solution for preparing drug release controlling layers) and a drug storing layer solution (a solution for preparing drug storing layers) respectively, and thereafter either 1) removing the organic solvents of the respective solutions by drying to prepare film-formed layers respectively, and mounting them, one on another, by a dry laminate or wet laminate method to prepare the desired multi-layered film preparation or 2) coating the drug storing layer solution on a film obtained by removing the organic solvent of the drug release controlling layer solution by drying, then removing the organic solvent by drying, and repeating these operations to prepare respective film-formed layers successively, thereby preparing the desired multi-layered film preparation.

The drug release controlling layer solution may be obtained by dissolving at least one water insoluble polymer compound and at least one plasticizer in an organic solvent and, when a transparent solution is formed, adding one or more water soluble polymer compounds thereto and dissolving it over an adequate period of time, and if desired, adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent and further allowing it to stand and adequately deaerating it.

The drug storing layer solution may be obtained, (i) by dissolving at least one water soluble polymer compound or a mixture of at least one water soluble polymer compound and at least one water insoluble polymer compound in an organic solvent and, when a transparent solution is formed, adding at least one plasticizer according to the desirability, and adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent, stirring uniformly, allowing it to stand and adequately deaerating it, (ii) by dissolving at least one water insoluble polymer compound and at least one plasticizer in an organic solvent, and when a transparent solution is formed, adding at least one water soluble polymer compound thereto and dissolving it over an adequate period of time, and adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent, stirring uniformly and further allowing it to stand and adequately deaerating it, or (iii) by dissolving at least one water soluble polymer compound and at least one plasticizer in an organic solvent and, when a transparent solution is formed, adding a prostaglandin solution containing or not containing an organic acid dissolved in an organic solvent, stirring uniformly and allowing it to stand and adequately deaerating it.

While the organic solvent to be used may be any one as long as it can dissolve the respective components for the preparation and is inert to them, methanol, ethanol, acetone and methylene chloride are preferred, and they may be used either alone or in combination.

As the drying method, a conventional method such as standing at room temperature, drying with moderate heating and fluidized bed drying can be used, but from the viewpoint of stability of prostaglandins drying at elevated temperatures is not proper. A temperature of between room temperature and 60°C is preferred. Therefore, it is preferred to dry using a device which can control the temperature and the air flow.

The size, shape and thickness of the multi-layered film preparation may be properly established depending on the pharmacological properties of the prostaglandin contained therein and the purpose for use, and may be prepared using a conventional process for producing multi-layered film preparations.

This invention is more fully described by the following examples and experiment examples but this invention should in no way be restricted thereto.

Exampl 1

1) Preparation f a drug release controlling layer s lution: 1.2 g f vinyl acetat resin, 200 mg of glycerin and 200 mg of triacetin were added to 40 ml of methanol and then stirred until transparent. Thereafter, 2.4 g of hydroxypropyl cellulose was added, and the solution was stirred and allowed to stand for effecting deaeration.

2) Preparation of a drug storing layer solution: 1.88 g of hydroxypropyl cellulose, 10 mg of glycerin and 100 mg of triacetin were added to 20 ml of methanol and stirred. To the resulting solution was added a solution of 10 mg of ONO-802 and 3 mg of tartaric anhydride in 10 ml of methanol, and the solution was stirred and then allowed to stand for effecting deaeration.

3) Production of multi-layered film preparations: A) 10 ml of the drug release controlling layer solution was dried at room temperature by a casting method, and then 15 ml of the drug storing layer solution was poured and similarly dried. Finally, 10 ml of the drug release controlling layer solution was poured and similarly dried to obtain a three-layered film preparation of about 0.9 mm in thickness. B) 10 ml portions of the drug release controlling layer solution were dried at room temperature using a casting method to obtain two films. The thus obtained two films were laminated with a film, obtained by similarly drying 15 ml of the drug storing layer solution, placed therebetween to obtain a three-layered film preparation of about 0.9 mm in thickness.

Example 2

A three-layered film preparation of about 0.9 mm in thickness was obtained similarly as in Example 1, except that the vinyl acetate resin employed in Example 1 was replaced by cellulose acetate, the hydroxypropyl cellulose by hydroxypropyl methyl cellulose and the glycerin by butyl phthalyl butyl glycolate.

Example 3

A three-layered film preparation of about 0.9 mm in thickness was obtained similarly as in Example 1, except that the hydroxypropyl cellulose employed in Example 1 was replaced by polyvinylpyrrolidone.

Example 4

1) Using 130 mg of vinyl acetate resin, 70 mg of glycerin, 70 mg of triacetin, 20 ml of methanol and 1.07 g of hydroxypropyl cellulose, similar procedures as in 1) and 3) B) of Example 1 were repeated to obtain two films.

2) 70 mg of vinyl acetate resin, 30 mg of glycerin and 30 mg of triacetin were added to 15 ml of methanol and stirred until transparent, after which 538.5 mg of hydroxypropyl cellulose was added and stirred. To this solution was added a solution of 1.5 mg of 16,16 - dimethyl - 6,9 - thio - PGI_1 methyl ester dissolved in 5 ml of methanol, and the solution was stirred and allowed to stand for effecting deaeration. The resulting solution was dried at room temperature by a casting method to obtain a film.

3) Using 1.26 g of hydroxypropyl cellulose, 65 mg of triacetin, 65 mg of glycerin, 15 ml of methanol, 2.5 mg of ONO-802, 2 mg of tartaric anhydride and 5 ml of methanol, similar procedures as in 2) and 3) B) of Example 1 were repeated to obtain two films.

4) Using a laminating method, the film obtained in 1), the film obtained in 3) the film obtained in 2), the film obtained in 3) and the film obtained 1) were laminated successively to obtain a five-layered film preparation of about 1.0 mm in thickness.

Example 5

A five-layered film preparation of about 1.0 mm in thickness was obtained similarly as in Example 4, except that the hydroxypropyl cellulose employed in Example 4 was replaced by polyvinylpyrrolidone.

Example 6

1) Using 300 mg of vinyl acetate resin, 150 mg of glycerin, 150 mg of triacetin, 30 ml of methanol, and 2.4 g of hydroxypropyl cellulose, similar procedures as in 1) of Example 1 were repeated to obtain about 30 ml of the solution.

2) A solution of 5 mg of ONO-802 and 1.5 mg of tartaric anhydride dissolved in one ml of methanol was added to 10 ml of the solution obtained in 1), stirred and then allowed to stand for effecting deaeration.

3) Using 20 ml of the solution obtained in 1) and the solution obtained in 2), procedures similar as in 3) B) of Example 1 were repeated to obtain a three-layered film preparation of about 0.9 mm in thickness.

Experiment Example 1

In order to compare the following preparations: the multi-layered film preparations produced in Examples 1 and 6; a single-layered film preparation employing a water soluble polymer compound (prepared as described her after; and simply referred to as HPC film); and a single-lay red film preparation empl ying a water solubl polymer compound and a water insoluble polymer c mpound (pr pared as described hereafter; and simply referred to as HPTG film), for the releas rate of the drug and the long-lasting properties of the release, a dissolution test was conducted according to the USP paddle method. The results of the experiment are sh wn in Table 1 and Fig. 2.

Preparation of HPC film

A s lution f 199.5 mg f hydroxypropyl cellulose in 2 ml f ethanol was stirred until a transparent solution was formed. The above cellulose solution was added to a solution f 0.2 mg of ONO-802 and 0.3 mg of tartaric anhydride in 1 ml of ethanol and th mixture was stirred uniformly. The solution thus obtained was dried at low temperature by a casting method to btain HPC film.

Preparation of HPTG film

A solution of 20 mg of vinyl acetate resin, 10 mg of glycerin and 10 mg of triacetin in 2 ml of methanol was stirred until a transparent solution was formed. 30 mg of HPC-M (a registered Trade Mark; and a kind of hydroxypropyl cellulose) and 130 mg of HPC-L (a registered Trade Mark; and a kind of hydroxypropyl cellulose) were added thereto and the solution was stirred uniformly. To the solution thus obtained was added a solution of 0.2 mg of ONO-802 and 0.3 mg of tartaric anhydride in 1 ml of methanol and the solution was stirred uniformly. The solution thus obtained was dried at room temperature by a casting method to obtain HPTG film.

TABLE 1

Percent dissolution (%) in various preparations

Sample	Dissolution time (hr) 0.5	1	2	3	4	5	6
HPC Film	97.6	100					
HPTG Film	23.1	57.0	98.3	100			
Film of Example 6	7.0	15.9	35.8	59.6	80.0	90.0	95.0
Film of Example 1	2.9	6.4	11.2	23.3	39.6	55.6	65.2

Experiment Example 2

The multi-layered film preparation produced in Example 1 and HPTG film were compared for the uterine contractile activity which is the pharmacological activity of ONO-802 in non-anesthetized rats. In this test, each preparation cut into a size corresponding to the indicated dosage was administered. The results of the experiment are shown in Table 2.

TABLE 2

Comparison of uterine contractile activity in various preparations (intravaginal administration to non-anesthetized rats)

Dosage of ONO-802 (μg/kg)	Film of Example 1		HPTG film	
	Effective Ex. /total Ex.	Duration (min.)	Effective Ex. /total Ex.	Duration (min.)
200	8/8	600—720	8/8	400—450
400	8/8	720—780	8/8	450—500
800	8/8	840—900	6/6	470—540

The duration of the uterine contractile activity was greatly prolonged with the preparation of Example 1. The intensity of the activity of HPTG film is greater than that of the preparation of Example 1 at the same dose. About 400 μg dosage of the preparation of Example 1 corresponded to the 100 μg dosage of HPTG film. In the case of the dosage levels of the preparation of Example 1, a weak pattern was exhibited at 200 μg, while medium-level lasting pattern were exhibited both at 400 and 800 μg.

Claims

1. A multi-layered film preparation having at least one drug-storing layer including at least one water-soluble polymer compound; drug release-contr lling layers disposed on pp site sides f th drug-storing lay r or layers, ach of said drug release-c ntrolling layers including at least one water-insoluble polymer compound at least one water-soluble polymer compound and at least on plasticizer; and a drug in said at least one drug-storing layer, characterized in that the drug is at least on prostaglandin and said drug-storing and drug-r leas controlling layers are formulat d so as to dissolve or

decompose totally during administration at a mucosal site, and the weight ratio of water-soluble polymer to water-insoluble polymer is in the range 9:1 to 1:1.

2. A multi-layered film preparation according to claim 1 which also includes at least one organic acid to stabilise said at least one prostaglandin.

3. A multi-layered film preparation according to claim 2 in which said at least one organic acid is selected from citric acid and tartaric acid.

4. A multi-layered film preparation according to claim 2 or 3, in which the organic acid is contained in a proportion of 0.01—0.5% of the preparation.

5. A multi-layered film preparation according to any preceding claim comprising more than one of said drug-storing layers.

6. A multi-layered film preparation according to any preceding claim which additionally contains at least one prostaglandin in at least one of the drug-release controlling layers.

7. A multi-layered film preparation according to any preceding claim, in which the or at least one of the drug-storing layers includes at least one plasticizer.

8. A multi-layered film preparation according to any preceding claim, in which the or at least one of the drug-storing layers includes at least one water-insoluble polymer compound.

9. A multi-layered film preparation according to any preceding claim, which has a surface area of 1.5—30 cm^2 and a thickness of 0.1—3 mm.

10. A multi-layered film preparation according to any preceding claim, in which said at least one water-soluble polymer compound is selected from hydroxypropyl cellulose, polyvinylpyrrolidone and hydroxypropyl methyl cellulose.

11. A multi-layered film preparation according to any preceding claim, in which said at least one water-insoluble polymer compound is selected from cellulose acetate and vinyl acetate resin.

12. A multi-layered film preparation according to any preceding claim, in which said at least one plasticizer is selected from diethyl phthalate, butyl phthalyl butyl glycolate, glycerin, triacetin, tributyrin, polyethylene glycol, polypropylene glycol, propylene glycol, diethylene glycol, triethylene glycol and dipropylene glycol.

13. A multi-layered film preparation according to any preceding claim, in which said at least one prostaglandin is selected from prostaglandin F, prostaglandin E and 6,9-thio-prostaglandin I_1.

14. A multi-layered film preparation according to any preceding claim, in which said at least one plasticizer is contained in a proportion of 10—30% of the preparation.

15. A three-layered film preparation according to claim 1 or 2, which has two drug release-controlling layers comprising vinyl acetate resin, glycerin, triacetin and hydroxypropyl cellulose, and therebetween one drug-storing layer comprising hydroxypropyl cellulose, glycerin, triacetin, 16,16 - dimethyl - trans - Δ^2 - PGE_1 methyl ester and tartaric anhydride.

16. A three-layered film preparation according to claim 1 or 2, which has two drug release-controlling layers comprising cellulose acetate, butyl phthalyl butyl glycolate, triacetin and hydroxypropyl methyl cellulose, and therebetween one drug storing layer comprising hydroxypropyl methyl cellulose, butyl phthalyl butyl glycolate, triacetin, 16,16 - dimethyl - trans - Δ^2 - PGE_1 methylester and tartaric anhydride.

17. A three-layered film preparation according to claim 1 or 2, which has two drug release-controlling layers comprising vinyl acetate resin, glycerin, triacetin and polyvinylpyrrolidone, and therebetween one drug-storing layer comprising polyvinylpyrrolidone, glycerin, triacetin, 16,16 - dimethyl - trans - Δ^2 - PGE_1 methyl ester.

18. A five-layered film preparation according to claim 1 or 2, which has the structure mounting successively (1) a drug release-controlling layer comprising vinyl acetate resin, glycerin, triacetin and hydroxypropyl cellulose, (2) a drug-storing layer comprising hydroxypyropyl cellulose, glycerin, triacetin, 16,16 - dimethyl - trans - Δ^2 - PGE_1 methyl ester, (3) a drug-storing layer comprising vinyl acetate resin, glycerin, triacetin, polyvinylpyrrolidone and 16,16 - dimethyl - 6,9 - thio - PGI_1 methyl ester, (4) the drug-storing layer as mentioned in (2), and (5) the drug-release-controlling layer as mentioned in (1).

19. A five-layered film preparation according to claim 1 or 2, which has the structure mounting successively (1) a drug release-controlling layer comprising vinyl acetate resin, glycerin, triacetin and polyvinylpyrrolidone, (2) a drug-storing layer comprising polyvinylpyrrolidone, glycerin, triacetin, 16,16 - dimethyl - trans - Δ^2 - PGE_1 methyl ester and tartaric anhydride, (3) a drug-storing layer comprising vinyl acetate resin, glycerin, triacetin, polyvinylpyrrolidone and 16,16 - dimethyl - 6,9 - thio - PGI_1 methyl ester, (4) the drug-storing layer as mentioned in (2), and (5) the drug-release-controlling layer as mentioned in (1).

20. A three-layered film preparation according to claim 1 or 2, which has two drug release-controlling layers comprising vinyl acetate resin, glycerin, triacetin and hydroxypropyl cellulose, and therebetween one drug-storing layer comprising vinyl acetate resin, glycerin, triacetin, hydroxypropyl cellulose, 16,16 - dimethyl - trans - Δ^2 - PGE_1 methyl ester and tartaric anhydride.

21. A process for producing a multi-layered film preparation including laminating (1) a film or films (drug-storing layer or layers) obtained by dissolving water-soluble polymer compound(s) and drug(s) in an organic solvent, optionally adding plasticizer(s) thereto, thoroughly stirring, and thereafter drying to remove the organic solvent, between (2) films (drug release-controlling layers) obtained by dissolving water-soluble polymer compound(s), water-insoluble polymer compound(s) and plasticizer(s) in an organic solvent, thoroughly stirring and thereafter drying to remove the organic solvent characterized in that said

drug(s) is or are prostaglandin(s) and in that said films are formulated so as to dissolve or d c mpose totally during administration at a mucosal site and the w ight ratio of water-soluble polymer to water-insoluble polymer is in the range 9:1 to 1:1.

22. A process as claimed in claim 21, wherein in the f rmation of the or at least one of the films forming the drug-storing layer or layers, wat r-insoluble p lymer compound(s) is or are dissolved in the organic solvent.

23. A process as claimed in claim 21 or 22, wherein prostaglandin(s) is or are included in at least one of the films forming the drug release-controlling layers.

24. A process as claimed in claim 21, 22 or 23, wherein organic acid(s) are included as stabilizer(s) for the prostaglandin(s).

Patentansprüche

1. Mehrschichtenfilm-Präparat mit wenigstens einer ein Arzneimittel aufbewahrenden Schicht, einschliessend wenigstens eine wasserlösliche Polymerverbinding; Arzneimittelabgabe-kontrollierende Schichten, die such an gegenüberliegenden Seiten der ein Arzneimittel aufbewahrenden Schicht oder Schichten befinden, wobei jede der die Arzneimittelabgabe kontrollierenden Schichten wenigstens eine wasserlösliche Polymerverbindung, wenigstens eine wasserunlösliche Polymerverbindung und wenigstens einen Weichmacher einschliessen; und einem Arzneimittel in wenigstens einer ein Arzneimittel aufbewahrenden Schicht, dadurch gekennzeichnet, dass das Arzneimittel wenigstens ein Prostaglandin ist und dass die die Arzneimittel aufbewahrenden und die die Arzneimittelabgabe kontrollierenden Schichten so formuliert sind, dass sie sich während der Verabreichung an einer Schleimhautstelle vollständig auflösen oder zersetzen und wobei das Gewichtsverhältnis von wasserlöslichem Polymer zu wasserunlöslichem Polymer im Bereich von 9:1 bis 1:1 liegt.

2. Mehrschichtenfilm-Präparat gemäss Anspruch 1, welches auch wenigstens eine organische Säure zum Stabilisieren des wenigstens einen Prostaglandins enthält.

3. Mehrschichtenfilm-Präparat gemäss Anspruch 2, in welchem die wenigstens eine Säure aus Citronensäure und Weinsäure ausgewählt ist.

4. Mehrschichtenfilm-Präparat gemäss Anspruch 2 oder 3, bei welchem die organische Säure in einem Anteil von 0,01 bis 0,5%, bezogen auf die Zubereitung, enthalten ist.

5. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, enthaltend mehr als eine der die Arzneimittel aufbewahrenden Schichten.

6. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, welches zusätzlich wenigstens ein Prostaglandin in wenigstens einer der die Arzniemittelabgabe kontrollierenden Schichten enthält.

7. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, in welchem wenigstens eine der die Arzneimittel aufbewahrenden Schichten wenigstens einen Weichmacher enthält.

8. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, in welchem die oder wenigstens eine der die Arzneimittel aufbewahrenden Schichten wenigstens eine wasserunlösliche Polymerverbindung enthält.

9. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, welches eine Oberfläche von 1,5 bis 30 cm^2 und eine Dicke von 0,1 bis 3 mm hat.

10. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, bei welchem die wenigstens eine wasserunlösliche Polymerverbindung ausgewählt ist aus Hydroxypropylcellulose, Polyvinylpyrrolidon und Hydroxypropylmethylcellulose.

11. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, in welchem die wenigstens eine wasserunlösliche Polymerverbindung ausgewählt ist aus Celluloseacetat und Vinylacetatharz.

12. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, in welchem der wenigstens eine Weichmacher ausgewählt ist aus Diethylphthalat, Butylphthalylbutylglycolat, Glycerin, Triacetin, Tributyrin, Polyethylenglykol, Polypropylenglykol, Propylenglykol, Diethylenglykol, Triethylenglykol und Dipropylenglykol.

13. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, in welchem das wenigstens eine Prostaglandin ausgewählt ist aus Prostaglandin F, Prostaglandin E und 6,9-Thioprostaglandin I_1.

14. Mehrschichtenfilm-Präparat gemäss einem der vorhergehenden Ansprüche, in welchem der wenigstens eine Weichmacher in einem Anteil von 10 bis 30%, bezogen auf die Zubereitung, vorliegt.

15. Dreischichtenfilm-Präparat gemäss Ansprüchen 1 oder 2, mit zwei die Arzneimittelabgabe kontrollierenden Schichten aus Vinylacetatharz, Glycerin, Triacetin und Hydroxypropylcellulose und dazwischen einer die Arzneimittel aufbewahrend n Schicht aus Hydroxypropylcellulose, Glycerin, Triacetin, 16,16 - Dimethyl - trans - Δ^2 - PGE_1 - methylester und Weinsäureanhydrid.

16. Dreischichtenfilm-Präparat gemäss Ansprüchen 1 oder 2, mit zwei di Arzneimittelabgab k ntrollier nden Schichten aus Cellul seacetat, Butylphthalylbutylglycolat, Triacetin und Hydroxypropylmethylcellulos und dazwischen einer die Arzneimittel aufbewahrenden Schicht aus Hydroxypropyl-

methylcellulose, Butylphthalylbutylglycolat, Triacetin, 16,16 - Dimethyl - trans - Δ^2 - PGE_1 - methylester und Weinsäureanhydrid.

17. Dreischichtenfilm-Präparat gemäss Ansprüchen 1 oder 2, mit zwei die Arzneimittelabgabe kontrollierenden Schichten aus Vinylacetatharz, Glycerin, Triacetin und Polyvinylpyrr lidon und dazwischen einer die Arzneimittel aufb wahrenden Schicht aus Polyvinylpyrrolidon, Glycerin, Triacetin, 16,16 - Dimethyl - trans - Δ^2 - PGE_1 - methylester.

18. Fünfschichtenfilm-Präparat gemäss Ansprüchen 1 oder 2, welches einen Aufbau hat, bei dem hintereinander aufgebaut sind (1) eine Arzneimittelabgabe-Kontrollschicht aus Vinylacetatharz, Glycerin, Triacetin und Hydroxypropylcellulose, (2) eine die Arzneimittel aufbewahrende Schicht aus Hydroxypropylcellulose, Glycerin, Triacetin, 16,16 - Dimethyl - trans - Δ^2 - PGE_1 - methylester, (3) eine die Arzneimittel aufbewahrende Schicht aus Vinylacetatharz, Glycerin, Triacetin, Polyvinylpyrrolidon und 16,16 - Dimethyl - 6,9 - thio - PGI_1 - methylester, (4) die in (2) erwähnte die Arzneimittel aufbewahrende Schicht und (5) die in (1) erwähnte die Arzneimittelabgabe kontrollierende Schicht.

19. Fünfschichtenfilm-Präparat gemäss Ansprüchen 1 oder 2, welches so aufgebaut ist, dass hintereinander aufgebracht sind (1) eine die Arzneimittelabgabe kontrollierende Schicht aus Vinylacetatharz, Glycerin, Triacetin, Polyvinylpyrrolidon, (2) eine die Arzneimittel aufbewahrende Schicht aus Polyvinylpyrrolidon, Glycerin, Triacetin, 16,16 - Dimethyl - trans - Δ^2 - PGE_1 - methylester und Weinsäureanhydrid, (3) eine die Arzneimittel aufbewahrende Schicht aus Vinylacetatharz, Glycerin, Triacetin, Polyvinylpyrrolidon und 16,16 - Dimethyl - 6,9 - thio - PGI_1 - methylester, (4) die in (2) erwähnte die Arzneimittel aufbewahrende Schicht und (5) die in (1) erwähnte die Arzneimittelabgabe kontrollierende Schicht.

20. Dreischichtenfilm-Präparat gemäss Ansprüchen 1 oder 2, mit zwei die Arzneimittelabgabe kontrollierenden Schichten aus Vinylacetatharz, Glycerin, Triacetin und Hydroxypropylcellulose, und dazwischen einer die Arzneimittel aufbewahrende Schicht aus Vinylacetatharz, Glycerin, Triacetin, Hydroxypropylcellulose, 16,16 - Dimethyl - trans - Δ^2 - PGE_1 - methylester und Weinsäureanhydrid.

21. Verfahren zur Herstellung eines Mehrschichtenfilm-Präparats, bei dem man (1) einen Film oder Filme (die Arzneimittel aufbewahrende Schicht oder Schichten), erhalten durch Auflösen von wasserlöslichen Polymerverbindung(en) und Arzneimittel(n) in einem organischen Lösungsmittel, gewünschtenfalls unter Zugabe von Weichmacher(n), gründlichem Rühren und anschliessendem Trocknen zur Entfernung des organischen Lösungsmittels, zwischen (2) Filmen (die Arzneimittelabgabe kontrollierenden Schichten) laminiert, wobei die die Arzneimittelabgabe kontrollierenden Schichten erhalten wurden durch Auflösen von wasserlöslichen Polymerverbindung(en), wasserunlöslichen Polymerverbindung(en) und Weichmacher(n) in einem organischen Lösungsmittel, gründlichem Rühren und anschliessendem Trocknen zur Entfernung des organischen Lösungsmittels, dadurch gekennzeichnet, dass das oder die Arzneimittel Prostaglandin oder Prostaglandine ist bzw. sind und dass die Filme so formuliert sind, dass sie sich während der Verabreichung an eine Schleimhautstelle vollständig auflösen oder zersetzen und wobei das Gewichtsverhältnis von wasserlöslichem Polymer zu wasserunlöslichem Polymer im Bereich von 9:1 bis 1:1 liegt.

22. Verfahren gemäss Anspruch 21, worin zur Bildung des oder wenigstens eines Films, welcher die Arzneimittel aufbewahrende Schicht oder Schichten bildet, wasserunlösliche Polymerverbindung(en) in den organischen Lösungsmitteln aufgelöst wird oder werden.

23. Verfahren gemäss Anspruch 21 oder 22, worin ein oder mehrere Prostaglandin(e) in wenigstens einer der die Arzneimittelabgabe kontrollierenden Schichten enthalten ist bzw. sind.

24. Verfahren gemäss Anspruch 21, 22 oder 23, worin organische Säure(n) als Stabilisator(en) für das oder die Prostaglandin(e) enthalten ist bzw. sind.

Revendications

1. Préparation pelliculaire multicouche comportant au moins une couche de magasinage de médicament comprenant au moins un composé polymère hydrosoluble; des couches de régulation de la libération du médicament disposées sur les côtés opposés de la couche ou des couches de magasinage de médicament, chacune desdites couches de régulation de la libération du médicament comprenant au moins un composé polymère hydrosoluble, au moins un composé polymère insoluble dans l'eau et au moins un plastifiant; et un médicament dans la ou les couches de magasinage de médicament, préparation caractérisée en ce que le médicament est au moins une prostaglandine, et les couches de magasinage de médicament et de régulation de la libération du médicament sont formulées de manière à se dissoudre ou à se décomposer totalement pendant l'administration sur un site de muqueuse, et le rapport pondéral entre le polymère hydrosoluble et le polymère insoluble dans l'eau se situe entre 9:1 et 1:1.

2. Préparation pelliculaire multicouche selon la revendication 1, qui comprend aussi au moins un acide organique pour stabiliser la u lesdites prostaglandin s.

3. Préparati n pelliculair multicouche selon la revendication 2, dans laquelle le ou l s acides rganiques est ou sont ch isis parmi l'acide citrique et l'acide tartrique.

4. Préparation pelliculaire multicouche selon la revendication 2 ou 3, dans laquelle l'acide organique est contenu en une pr portion représentant de 0,01 à 0,5% de la préparation.

5. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, comprenant plus d'une desdites couches de magasinage de médicament.

6. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, qui contient en outre au moins une prostaglandine dans l'une au moins des couches de régulation de la libération du médicament.

7. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle la ou au moins une des couches de magasinage de médicament comprend au moins un plastifiant.

8. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle la ou au moins une couche de magasinage de médicament comprend au moins un composé polymère insoluble dans l'eau.

9. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, qui a une aire de surface de 1,5 à 30 cm^2 et une épaisseur de 0,1 à 3 millimètres.

10. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle le ou les composé(s) polymère(s) hydrosoluble(s) est ou sont choisi(s) parmi l'hydroxypropyl cellulose, la polyvinylpyrrolidone et l'hydroxypropyl méthyl cellulose.

11. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle ledit ou lesdits composé(s) polymère(s) insoluble(s) dans l'eau est ou sont choisi(s) parmi l'acétate de cellulose et de la résine d'acétate de vinyle.

12. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle ledit ou lesdits plastifiants est ou sont choisi(s) parmi le phtalate de diéthyle, du butyl glycolate de butyle et de phtalyle, du glycérol, de la triacétine, de la tributérine, du polyéthylène glycol, du polypropylène glycol, du propylène glycol, du diéthylène glycol, du triéthylène glycol et du dipropylène glycol.

13. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle ladite prostaglandine ou les prostaglandines est ou sont choisie(s) parmi la prostaglandine F, la prostaglandine E, et la 6,9-thio-prostaglandineI_1.

14. Préparation pelliculaire multicouche selon l'une quelconque des revendications précédentes, dans laquelle ledit ou lesdits plastifiants est ou sont contenu(s) en une proportion representant 10 à 30% de la préparation.

15. Préparation pelliculaire en trois couches selon la revendication 1 ou 2, qui comporte deux couches de régulation de la libération de médicament, comprenant de la résine d'acétate de vinyle, du glycérol, de la triacétine et de l'hydroxypropyl cellulose et, entre ces deux couches, une couche de magasinage de médicament comprenant de l'hydroxypropyl cellulose, du glycérol, de la triacétine, de l'ester méthylique de 16,16 - diméthyl - trans - Δ^2 - PGE_1 et de l'anhydride tartrique.

16. Préparation pelliculaire en trois couches selon la revendication 1 ou 2, qui comporte deux couches de régulation de la libération du médicament, comprenant de l'acétate de cellulose, du butyl glycolate de butyle et de phtalyle, de la triacétine et de l'hydroxypropyl méthyl cellulose et, entre ces deux couches, une couche de magasinage de médicament comprenant de l'hydroxypropyl méthyl cellulose, du butyl glycolate de butyle et de phtalyle, de la triacétine, de l'ester méthylique de 16,16 - diméthyl - trans - Δ^2 - PGE_1 et de l'anhydride tartrique.

17. Préparation pelliculaire en trois couches selon la revendication 1 ou 2, qui comporte deux couches de régulation de la libération du médicament, comprenant de la résine d'acétate de vinyle, du glycérol, de la triacétine et de la polyvinylpyrrolidone et, entre ces deux couches, une couche de magasinage de médicament comprenant de la polyvinylpyrrolidone, du glycérol, de la triacétine, de l'ester méthylique de 16,16 - diméthyl - trans - Δ^2 - PGE_1.

18. Préparation pelliculaire en cinq couches selon la revendication 1 ou 2, qui comporte une structure présentant successivement (1) une couche de régulation de la libération du médicament, comprenant de la résine d'acétate de vinyle, du glycérol, de la triacétine, et de l'hydroxypropyl cellulose, (2) une couche de magasinage de médicament comprenant de l'hydroxypropyl cellulose, du glycérol, de la triacétine, de l'ester méthylique de 16,16 - diméthyl - trans - Δ^2 - PGE_1, (3) une couche de magasinage de médicament comprenant de la résine d'acétate de vinyle, du glycérol, de la triacétine, de la polyvinylpyrrolidone et de l'ester méthylique de 16,16 - diméthyl - 6,9 - thio - PGI_1, (4) la couche de magasinage de médicament telle que mentionnée en (2), et (5) la couche de régulation de la libération de médicament telle que mentionnée en (1).

19. Préparation pelliculaire en cinq couches selon la revendication 1 ou 2, qui comporte la structure présentant successivement (1) une couche de régulation de la libération du médicament, comprenant de la résine d'acétate de vinyle, du glycérol, de la triacétine et de la polyvinylpyrrolidone, (2) une couche de magasinage de médicament comprenant de la polyvinylpyrrolidone, du glycérol, de la triacétine, de l'ester méthylique de 16,16 - diméthyl - trans - Δ^2 - PGE_1 et de l'anhydride tartrique, (3) une couche de magasinage de médicament comprenant de la résine d'acétate de vinyle, du glycérol, de la triacétine, de la polyvinylpyrrolidone et de l'ester méthylique de 16,16 - diméthyl - 6,9 - thio - PGI_1, (4) la couche de magasinage de médicament telle que mentionnée en (2), et (5) la couche de régulation de la libération du médicament telle que mentionnée en (1).

20. Préparation pelliculaire en trois couches selon la revendication 1 ou 2, qui comporte deux couches de régulation de la libération de médicament comprenant de la résine d'acétate de vinyle, du glycérol, de la

triacétine et de l'hydroxypropyl cellulose et, entre ces deux couches, une couche de magasinage de médicament comprenant de la résine d'acétat de vinyle, du glycérol, de la triacétine, de l'hydroxypropyl cellulose, d l'ester méthylique de 16,16 - diméthyl - trans - Δ^2 - PGE_1 et de l'anhydride tartrique.

21. Procédé pour produire une préparation pelliculaire multicouche, comprenant la stratification de (1) une ou des pellicules (couche(s) de magasinage de médicament) que l'on obtient en dissolvant un ou des composés polymères hydrosolubles et un ou des médicaments dans un solvant organiqu, en ajutant éventuellement un ou des plastifiants, en agitant de façon poussée puis en sèchant pour enlever le solvant organique, (2) des pellicules (couches de régulation de la libération de médicament) que l'on obtient en dissolvant un ou des composés polymères hydrosolubles, un ou des composés polymères insolubles dans l'eau et un ou des plastifiants dans un solvant organique, en agitant de façon poussée puis en sèchant pour enlever le solvant organique, procédé caractérisé en ce que le ou lesdits médicaments est ou sont une ou des prostaglandines, et en ce qu'on formule lesdites pellicules de manière à se dissoudre ou à se décomposer totalement pendant l'administration sur un site de muqueuse, et en ce que le rapport pondéral du polymère hydrosoluble au polymère insoluble dans l'eau se situe entre 9:1 et 1:1.

22. Procédé selon la revendication 21, dans lequel, lors de la formation de la ou d'au moins une des pellicules formant la ou les couches de magasinage du médicament, un dissout, dans le solvant organique, le ou les composé(s) polymère(s) insoluble(s) dans l'eau.

23. Procédé selon la revendication 21 ou 22, dans lequel la ou les prostaglandines est ou sont incluses dans au moins l'une des pellicules qui forment les couches de régulation de la libération du médicament.

24. Procédé selon la revendication 21, 22 ou 23, dans lequel un ou des acides organiques est ou sont inclus à titre de stabilisant(s) de la ou des prostaglandines.

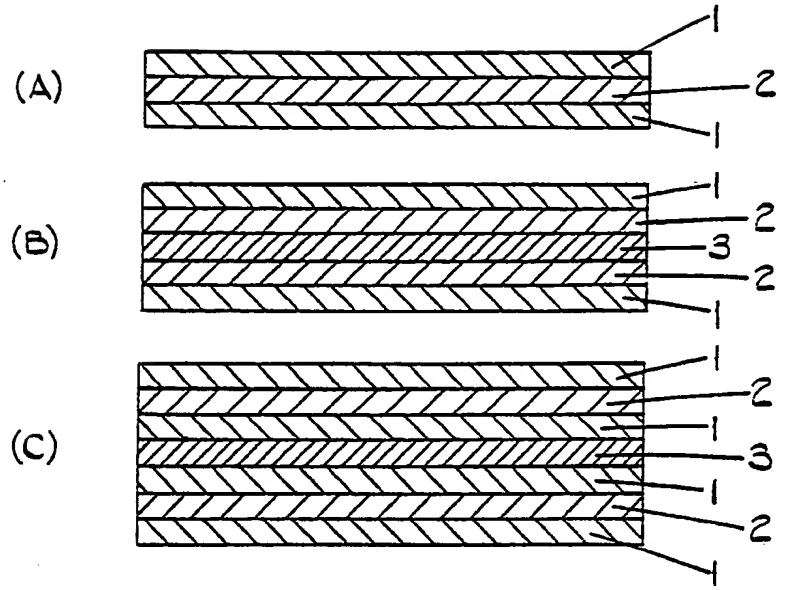


FIG.1.

LAYER 1 : DRUG RELEASE CONTROLLING LAYER
LAYER 2 AND LAYER 3 : DRUG STORING LAYER

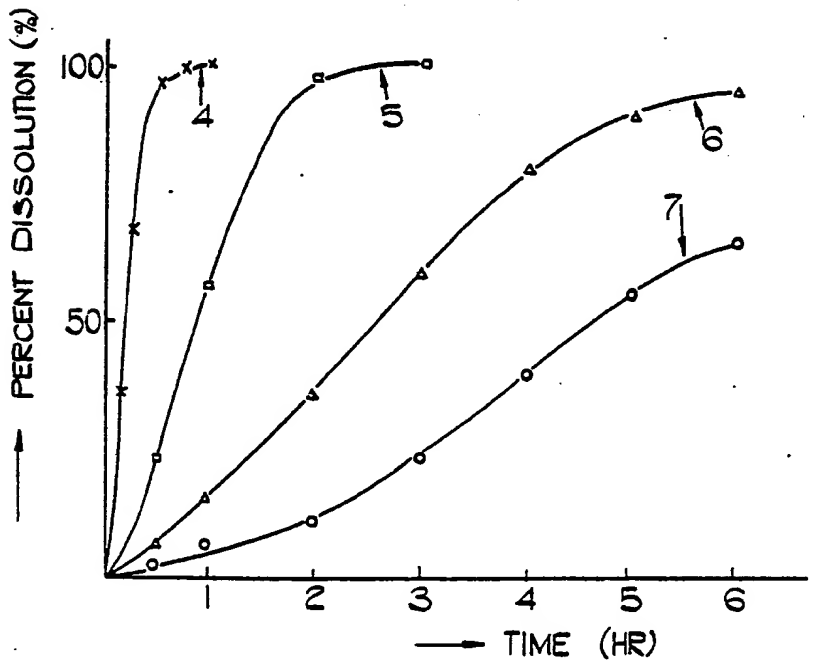


FIG.2.

4: HPC FILM PREPARATION
5: HPTG FILM PREPARATION
6: FILM PREPARATION OF EXAMPLE 6
7: FILM PREPARATION OF EXAMPLE 1